Paper No. 28

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte RUDOLF GLOCKSHUBER, MARTINA WUNDERLICH,
ARNE SKERRA, and RAINER RUDOLPH

_____

Appeal No. 1996-1085
Application No. 08/097,621

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ON BRIEF

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Before ROBINSON, SPIEGEL, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 32-59 that are all the claims pending in the application.

Claim 32 is illustrative of the subject matter on appeal and is reproduced below:

> 32. A process for increasing the formation of the natural protein conformation when disulfide bonded proteins are secreted by an E.coli host that contains a recombinant DNA coding for the secreted protein, comprising culturing the host in a suitable culture medium in the presence of oxygen under conditions suitable for the expression of the recombinant DNA, wherein said culture medium contains 0.1 to 20 mmol/l of one or more thiol reagents.

The references relied upon by the examiner are:

Pigiet et al. (Pigiet) 4,904,602 February 27, 1990

Bowden et al. (Bowden), "Folding and Aggregation of β-Lactamase in the Periplasmic Space of Escherichia coli," The Journal of Biological Chemistry, Vol. 265, No. 28, pp. 16760-766 (1990)

Hiram F. Gilbert (Gilbert), Advances in Enzymology, Vol. 63, pp. 70-74, and 144-46 (Alton Meister ed. , John Wiley & Sons 1990)

Appellants rely on the following references:

Wetlaufer et al. (Wetlaufer), "The oxidative folding of proteins by disulfide plus thiol does not correlate with redox potential," Protein Engineering, Vol. 1, No. 2, pp. 141-46 (1987)

Gething et al., "Protein folding in the cell," Nature, Vol. 355, pp.33-45 (1992)

Bardwell et al., "A pathway for disulfide bond formation in vivo," Proc. Natl. Acad. Sci. USA, Vol. 90, pp. 1038-1042 (1993)

Missiakas et al. (Missiakas), "Identification and characterization of the Escherichia coli gene dsbB, whose product is involved in the formation of disulfide bonds in vivo," Proc. Natl. Acad. Sci. USA, Vol. 90, pp. 7084-088 (1993)

GROUNDS OF REJECTION

Claims 32-52 are rejected under 35 U.S.C. § 103 as being unpatentable over Bowden and Gilbert.

Claims 53-59 are rejected under 35 U.S.C. § 103 as being unpatentable over Bowden and Gilbert as applied to claims 32-52 and further in view of Pigiet.

We reverse.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner. We make reference to the Examiner's Answer[1], and the Supplemental Examiner's Answer[2] for the examiner's reasoning in support of the rejection. We further reference appellants' Brief[3], and appellants' Reply Brief[4] for the appellants' arguments in favor of patentability.

Rejections under 35 U.S.C. § 103:

Obviousness is a legal conclusion based on the underlying facts. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966); Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1270, 20 USPQ2d 1746, 1750 (Fed. Cir. 1991); Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1595-97 (Fed. Cir. 1987), cert. denied, 481

[1] Paper No. 25, mailed February 8, 1995.
[2] Paper No. 27, mailed July 17, 1995.
[3] Paper No. 24, received November 8, 1994.
[4] Paper No. 26, received April 10, 1995.

U.S. 1052 (1987). The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

The combination of Bowden and Gilbert:

The examiner applies Bowden (Answer, page 4) to teach "'the permeability of the outer membrane of E. coli … the redox potential, pH, and ionic composition of the periplasmic space varies [sic] depending on the extracellular environment.'" The examiner then applies Gilbert (Answer, page 4) to teach "protein conformation is in part dependent on the thiol-disulfide redox state of the immediate environment."

From these teachings, the examiner reasons (Answer, page 5) that given the teachings of Bowden and Gilbert it "would have been obvious to one of ordinary skill in the art to use oxidizing thiol-reagents (i[.]e. GSH and GSSH) in the extracellular environment (i[.]e. the culture medium) to alter the redox potential of the periplasmic space, thus optimizing the conditions for correct folding of secreted proteins." We note that neither Bowden nor Gilbert teach the addition of thiol-reagents to culture medium to adjust the redox potential of the periplasmic space. Further, assuming arguendo that the prior art suggested adding a thiol-reagent to the culture medium, the examiner has not identified, and we do not find, where the prior art discloses or suggests that the external membrane of the E. coli cell is sufficiently permeable to provide a sufficient amount of the thiol reagent in its periplasmic space.

It is well established that to establish a prima facie case of obviousness, there must be both (1) a suggestion or motivation to modify the references or

combine reference teachings, and (2) a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

In our judgment, based on the evidence of record, the only reason or suggestion to modify the references to arrive at the present invention with a reasonable expectation of success comes from appellants' specification.

Therefore, we find that the examiner failed to meet his burden of establishing a prima facie case of obviousness. Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Accordingly, we reverse the rejection of claims 32-52 under 35 U.S.C. § 103 as being unpatentable over Bowden and Gilbert.

The combination of Bowden and Gilbert in view of Pigiet:

The examiner applies Pigiet (Answer, page 6) to teach that E. coli thioredoxin shufflease is involved in protein folding. However, Pigiet fails to make up the deficiencies of Bowden and Gilbert, supra.

Therefore, we find that the examiner failed to meet his burden of establishing a prima facie case of obviousness. Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. Fine, 837 F.2d at 1074, 5 USPQ2d at 1598.

Accordingly, we reverse the examiner's rejection of claims 53-59 under 35 U.S.C. § 103 as being unpatentable over Bowden and Gilbert as applied to claims 32-52 and further in view of Pigiet.

REVERSED

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| Douglas W. Robinson | ) |
| Administrative Patent Judge | ) |
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| | ) |
| | ) BOARD OF PATENT |
| Carol A. Spiegel | ) |
| Administrative Patent Judge | ) APPEALS AND |
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| | ) INTERFERENCES |
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| Donald E. Adams | ) |
| Administrative Patent Judge | ) |

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